Seizure 27 (2015) 10–15

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Heart rate variability in infants with West syndrome

Michelle Mai Møller [a,*], Hans Høgenhaven [b,1], Peter Uldall [c], Martin Ballegaard [d]

[a] University Hospital Rigshospitalet, Blegdamsvej 9, DK 2100 Copenhagen, Denmark
[b] Odense University Hospital, Department of Neurology, Søndre Boulevard 29, DK 5000 Odense C, Denmark
[c] Copenhagen University, Clinic of Children and adolescence, Rigshospitalet, Blegdamsvej 9, DK 2100 Copenhagen, Denmark
[d] Department of Clinical Neurophysiology, Rigshospitalet, DK 2100 Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 9 September 2014
Received in revised form 24 January 2015
Accepted 3 February 2015

Keywords:
West syndrome
Heart rate variability
Autonomic function
Infantile spasms
Hypsarrhythmia

ABSTRACT

Purpose: West syndrome (WS) is a severe age-related acute epileptic encephalopathy of infancy characterized by infantile spasms, hypsarrhythmia and psychomotor delay. The aim of this study was to investigate if patients with WS had an altered autonomic output to the heart.
Methods: In 23 patients with WS the heart rate variability (HRV) was investigated by examining time- and frequency-domain parameters of HRV at the time of the diagnosis of hypsarrhythmia and compared to 22 age-matched controls. For the WS patients the same dataset was obtained and compared again at the end of the study period, when hypsarrhythmia was no longer present.
Results: Compared to controls, patients with WS during hypsarrhythmia had significantly lower SDNN (the standard deviation of the NN interval, i.e. the square root of variance) (19.2 ms; $p = 0.007$, Mann–Whitney's *U*-Test) and total power (242 ms^2; $p = 0.044$, Mann–Whitney's *U*-Test) in the awake state, indicating an abnormal autonomic output to the heart. Comparing the initial to the final examination demonstrated a significant increase in the HRV parameters SDNN (31.3 ms) and total power (757 ms^2; $p = 0.001$ and $p = 0.013$, Wilcoxon Signed Ranked Test). In addition, at the final examination the WS-patients no longer differed significantly from the controls.
Conclusion: Our data suggest that the initial reduction in HRV in patients at the time of onset of WS is transient and related to the presence of hypsarrhythmia.

1. Introduction

West syndrome (WS) is a severe age-related acute epileptic encephalopathy of early infancy. WS consists of the triad epileptic (infantile) spasms, the abnormal electroencephalographic (EEG) pattern of hypsarrhythmia and psychomotor delay [1].

Heart rate variability (HRV) serves as a useful and accepted marker of the sympathetic–parasympathetic balance of the autonomic nervous system to the heart. Low HRV is often an indicator of abnormal and insufficient modulation from the autonomic nervous system [2].

Epileptic seizures can induce changes in the balance between sympathetic and parasympathetic influence on the heart including an acute autonomic dysfunction suspected to play a role in sudden unexpected death in epilepsy (SUDEP) [2–12], and it has been suggested that a high sympathetic tone ictally and interictally is the main cause of lower HRV and SUDEP [2,3].

A previous study with frequency-domain analysis of HRV in children with West syndrome found patients to have a more prominent low frequency component of HRV, suggesting a higher sympathetic tone compared to controls [13].

In this study we investigated if hypsarrhythmia in West syndrome may induce an altered autonomic output to the heart by analysing 5-min segments of electrocardiogram (ECG) recorded routinely together with the video-EEG at the time of diagnosis. The RR-intervals were analysed in the time- and frequency-domain and data were compared with data from age-matched controls. At the end of the study period, when the WS patients no longer had the EEG pattern of hypsarrhythmia or clinical spasms, HRV data were re-analysed and compared to baseline values. Finally it was investigated if possible alterations might have a correlation to the clinical outcome.

To the best of our knowledge this is the first study to investigate how the autonomic nervous system to the heart is affected over time in patients with WS.

* Corresponding author. Tel.: +45 25210828.
E-mail addresses: michelle.mai.moller@gmail.com (M.M. Møller), hans.hoegenhaven@rsyd.dk (H. Høgenhaven), pu@rh.dk (P. Uldall), martin.ballegaard@regionh.dk (M. Ballegaard).
[1] Previously at: Department of Clinical Neurophysiology 3063, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, DK 2100 Copenhagen, Denmark.

http://dx.doi.org/10.1016/j.seizure.2015.02.003
1059-1311/

2. Methods

2.1. Patients

Twenty-three infants (11 females and 12 males, median age 6 months, range 3–15 months), diagnosed with West syndrome, who were seen at the Department of Clinical Neurophysiology from January 2005 through January 2012, were included in this retrospective study. No patients were lost to follow up. Inclusion criteria were an EEG showing hypsarrhythmia and a simultaneous ECG of good quality. Routinely, the patients were followed with serial EEGs to monitor the effect of treatment.

Patients were excluded if they had a story of heart disease or conduction abnormalities on the ECG or if they were prescribed with antiarrhythmic agents.

At the initial recording some patients were treated with antiepileptic drugs but no patients had started treatment with glucocorticoids.

2.2. Controls

Twenty-two age- and sex-matched infants (13 males, 9 females, median age 6 months, range 3–14 months), who were referred under the suspicion of having epilepsy but had a normal EEG and finally were diagnosed as healthy, served as a control group.

2.3. EEG and ECG measurements

All EEGs were of minimum 30 min duration using the international 10/20 system electrode array recorded on standard digital commercial equipment. Almost all had simultaneous video-recording to document clinical events. The historical recordings were re-analysed by a neurophysiologist (HH) to confirm the original finding and to select characteristic epochs of hypsarrhythmia (chaotic pattern, high EEG-amplitude, epileptic discharges, seizure patterns and/or series of infantile spasms from the EEG and the simultaneous video). 5 min-segments of ECG-recordings between seizures, awake and during sleep, were also selected. Sleep was judged from the video and characteristic EEG findings, if present. An evaluation of sleep stage was not possible at time of diagnosis, due to the setting and severely abnormal EEG pattern.

2.4. Measurement and analysis of HRV

Heart rate variability (HRV) was calculated from the duration of RR intervals in the 5 min-ECG segment analysed. The RR interval durations were measured using the programme LabChart 7 (Version 7.3.2) after automatic QRS complex detection (peak determination method). All detected QRS complexes were verified manually and corrected for artefacts. QRS complexes were classified into normal or ectopic beats.

The tachygram (graphic presentation of RR-interval) was visually inspected to detect trends in the data, ectopic beats or other sudden changes, which could disturb especially the frequency analysis.

The recording was graded using a score of 0 (no disturbances), 1 (less than 2% of aberrant beats), 2 (aberrant beats during less than 1/3 of the time series) or 3 (aberrant beats during more than 1/3 of the time series). Recordings with a score of 1 and 2 were included in all analyses while the rest were excluded from the analysis in the frequency domain.

Analysis of heart rate variability in the time- and frequency domains were done according to the standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [14].

After QRS complex detection, the normal-to-normal (NN) interval (i.e. all intervals between adjacent QRS complexes resulting from sinus node depolarisations) was determined. The R-wave peak was identified without any change to the recorded signal due to the high signal-to-noise ratio in these recordings.

In the time domain median heart rate (beats per minute) and SDNN (the standard deviation of the NN interval, i.e. the square root of variance) were measured. SDNN is a statistical estimate of overall HRV and reflects all the cyclic components responsible for variability in the 5-min ECG recording [14]. As a substantial occurrence of aberrant beats will affect the statistical analysis, the SDNN was reported for the entire group of patients and, in addition, for the group of patients with recordings scored 0 and 1, only.

In the frequency domain, spectral analysis of heart rate can provide additional information on the autonomic function of the heart. Power spectral density (PSD) analysis provides the basic information of how power (i.e. variance) is distributed as a function of frequency [14]. Frequency domain analysis was performed using the non-parametric method of Fast Fourier Transformation (FFT) with a Welch-window correction (formal). The total power of the dataset was divided into the power of variability in three standard frequency bands including high frequency band (HF) ranging from 0.3 to 1.3 Hz, low frequency band (LF, 0.04–0.3 Hz), very low frequency band (VLF $\leq$ 0.04 Hz). The high frequency band limits were adjusted to match infant respiratory sinus arrhythmia. In addition, power in the low- and high-frequency bands were reported normalized to the total power (n.u.: LF/(Total power − VLF) × 100) and as the low-frequency/high-frequency ratio (LF/HF). Vagal activity is the major contributor to the HF component, while the LF component is considered by some authors as a marker of sympathetic modulation and by others as a parameter including both vagal and sympathetic influences [14].

2.5. Statistical methods

The data were analysed using the statistical package SPSS-20.0 for Mac. Descriptive statistics were given as medians (range) due to the small number of individuals in each study group. A value of p less than 0.05 was considered statistically significant. Normality of the distribution of data was assessed using the Kolmogorov–Smirnov test, which suggested violation of the assumption of normality. As a result, the non-parametric Mann–Whitney's U-test was applied for between-groups comparisons. In order to analyse the change in the weekly recordings we tried to perform an ANOVA, but this was not possible due to missing data points. For that reason only the first- and last EEG recording were included and compared using the Wilcoxon Signed Rank Test.

The occurrence of aberrant beats in the recordings giving scores 0–3 were compared between groups. The distribution of scores among the patients was compared to the distribution among controls using the Mann–Whitney's U-test.

2.6. Ethics

The retrospective data collection has been approved by The Danish Data Protection Agency (No. 2007-58-0015).

3. Results

Clinical characteristics of the 23 patients with West syndrome (WS) are shown in Table 1. Median age at onset was 6 months (3–15 m). No significant difference in gender and age between the study group and the control group was found. The diagnostic work-up showed that 15 had symptomatic WS and 8 had cryptogenic

Table 1
Profiles of patients with West syndrome.

Patient no.	Aetiology	Age at onset	Medication during study period	Clinical outcome
1	Periventricular leukomalacia	6	VGT	1
2	Cryptogenic	6	VGT, HCS, KGD, TPM, CZP	2
3	Cryptogenic	6	VGT, HCS, KGD	2
4	Cryptogenic	5	VGT, HCS	2
5	Cryptogenic	4	VGT, HCS	1
6	Fetal hypoxia	3	VGT, HCS, OXC	2
7	Tuberous sclerosis	8	VGT, TPM	2
8	Specific gene mutation	4	VGT, HCS, TPM, KGD	2
9	Perinatal haemorrhage	4	VGT, HCS, TPM, VPA, CZP	2
10	Periventricular leukomalacia	5	VGT, HCS, KGD, LEV	2
11	Tuberous sclerosis	6	VGT, HCS	1
12	Miller Diekers syndrome	6	VGT, HCS, OXC	2
13	Cryptogenic	4	VGT, HCS, KGD	2
14	Cortical dysplasia	5	VGT	2
15	Cryptogenic	7	VGT, HCS	1
16	Cryptogenic	7	VGT, HCS	1
17	Periventricular leukomalacia	8	VGT, HCS, LEV, TPM	2
18	Perinatal haemorrhage	8	VGT	2
19	Cortical dysplasia	4	VGT, HCS, OXC	2
20	Cryptogenic	10	VGT, HCS, VPA	1
21	Tuberous sclerosis	4	VGT	1
22	Tuberous sclerosis	5	VGT, TPM	2
23	Down's syndrome	15	VGT, HCS	2

VGT, vigabatrin; HCS, hydrocortisone; KGD, ketogenic diet; TPM, topiramat; CZP, clonazepam; OXC, oxcarbazepine; VPA, valproate; LEV, levetiracetam clinical outcome: 1 = good, almost age-appropriate development (development corresponding to 70% or more); 2 = mental and/or physical retardation of varying degree.

WS. 7 children had a normal or almost age-appropriate development, while 16 had mental and/or physical retardation of varying degree at follow up (Table 1).

At the time of the first recording some of the children had just started treatment with vigabatrin but none of the children had started hydrocortisone (Table 1).

All 23 patients had hypsarrhythmia in their EEG at presentation (week 1). After 2 weeks 10 patients continued to have hypsarrhythmia. The number of patients with hypsarrhythmia gradually decreased to two patients after 6 weeks. Seven patients presented clinically with infantile spasms during their first EEG recording, while one patient had infantile spasms documented in EEG after 2 weeks and in the following 6 weeks (Fig. 1). Two patients, who still showed hypsarrhythmia after 6 weeks, continued to present very abnormal hypsarrhythmia-like EEG patterns after 18 and 22 months, respectively, after which their diagnoses were changed to a chronic encephalopathy syndrome.

Ten patients presented normalization in their last EEG recording, while the remaining thirteen continued to have other types of epileptiform abnormalities.

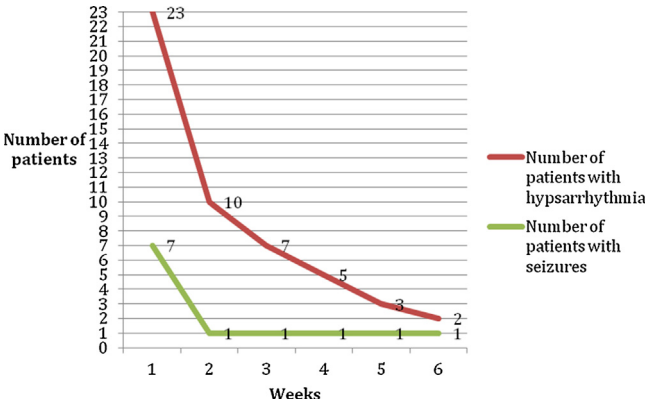

Fig. 1. Number of patients with hypsarrhythmia (red) and seizures (green) during the first 6 weeks after presentation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

At the time of diagnosis the ECG showed sinus rhythm in all patients with WS. The median heart rate in the patients was 142 beats per minute (bpm) (111–196) when awake and 125 bpm (100–157) during sleep. The controls had values of 139 bpm (103–158) when awake and 123 bpm (92–144) during sleep, which did not differ significantly from that of the patients ($p = 0.205$ and $p = 0.721$).

During the recordings no ectopic beats (characterized by a shortened RR-interval followed by a compensatory increased RR-interval) were seen. However in some recordings episodic changes were found to disturb the recording, giving a sudden increase in RR-interval and followed by a smaller increase in RR-interval of the subsequent beats. Those changes were compatible with a sudden change in sinoatrial conduction time. The first recordings during the awake state had significantly lower scores of aberrant beats in patients compared to controls ($p = 0.036$). During sleep this difference was not significant ($p = 0.453$). Recordings at the end of the study did not differ significantly in neither the awake state or during sleep ($p = 0.359$ and $p = 0.344$). The distribution of scores is shown in Table 2.

Comparisons of HRV characteristics between patients with WS and control subjects during wakefulness are shown in Table 3 and during sleep in Table 4.

Table 2
Number of ECG-recordings with episodes of aberrant beats and the distribution of recordings according to their score in the patients on their first visit, on their last visit and the score in controls. The scores were given both for recordings during the awake state and during sleep.

	Patients – first visit		Patients – last visit		Controls	
Score	Awake	Sleep	Awake	Sleep	Awake	Sleep
0	15	4	6	4	7	9
1	4	3	8	4	9	5
2	1	6	5	2	5	6
3	2	1	4	4	1	2
Total	22	14	23	14	22	22

Table 3
Comparison of heart rate variability parameters during wakefulness in the patients with West syndrome and controls.

	Controls ($n=22$)	Patients: first EEG-recording ($n=23$)	Patients: last EEG-recording ($n=23$)	**P1** Comparison between the patients' first EEG recording and the controls	**P2** Comparison between the patients' first EEG recording and their last EEG recording	**P3** Comparison between the patients' last EEG recording and the controls
SDNN (ms)	**31.0** (14.6–79.1)	**19.2** (7.6–57.2)	**31.3** (16.5–106)	**0.007**	**0.001**	**0.482**
SDNN* (ms)	**25.1** (14.6–50.7)	**18.2** (7.6–42.6)	**27.6** (16.5–63.7)	**0.054**	**0.028**	**0.569**
Total power (ms^2)	**659** (167–2130)	**242** (54–1643)	**757** (192–3847)	**0.044**	**0.013**	**0.380**
LF_{norm} (n.u.)	**84.5** (58.3–94.6)	**81** (62–90)	**60.1** (16.5–81.8)	**0.661**	**0.753**	**0.559**
HF_{norm} (n.u.)	**15.5** (5.4–41.7)	**19** (10.4–38)	**20.8** (7.1–41.4)	**0.661**	**0.753**	**0.792**
LF/HF	**5.5** (1.4–17.5)	**4.2** (1.6–8.6)	**2.7** (0.4–11.5)	**0.661**	**0.463**	**0.726**
Heart rate (bpm)	**139** (103–158)	**142** (111–196)	**120** (88–172)	**0.205**	**0.002**	**0.107**

Data are expressed as medians (range). SDNN, the standard deviation of the NN interval (all patients); SDNN* (patients without aberrant heart beats); LF_{norm}, low frequency power in normalized unit (LF/LF + HF); HF_{norm}, high frequency power in normalized unit (HF/HF + LF); LF/HF, ratio of LF component to HF component. P1: *p*-value obtained using Mann–Whitney's *U*-test. P2: *p*-value obtained using Wilcoxon test. P3: *p*-value obtained using Mann–Whitney's *U*-test.

Table 4
Comparison of heart rate variability parameters during sleep in the patients with West syndrome and controls.

	Controls ($n=22$)	Patients: first EEG-recording ($n=15$)	Patients: last EEG-recording ($n=13$)	**P1** Comparison between the patients' first EEG recording and controls	**P2** Comparison between the patients' first EEG recording and their last EEG recording	**P3** Comparison between the patients' last EEG recording and controls
SDNN (ms)	**31.0** (7.9–98.6)	**31.5** (12.4–75.3)	**47.4** (16.9–107.2)	**0.846**	**0.037**	**0.048**
SDNN* (ms)	**24.4** (7.9–98.6)	**17.7** (12.4–38)	**38.4** (16.9–41.8)	**0.243**	**0.285**	**0.529**
Total power (ms^2)	**592** (65–9660)	**311** (152–861)	**1496** (328–1592)	**0.203**	**0.285**	**0.378**
LF_{norm} (n.u.)	**71** (14.9–92.5)	**77.7** (68.9–82.7)	**21.3** (10.1–84.7)	**0.457**	**0.593**	**0.900**
HF_{norm} (n.u.)	**29** (7.5–85.1)	**18** (15.3–25.9)	**26.2** (9.9–54)	**0.339**	**0.593**	**0.529**
LF/HF	**2.5** (0,2–12.3)	**4.4** (2.9–4.8)	**1.4** (0.2–8.6)	**0.339**	**1.000**	**1.000**
Heart rate (bpm)	**123** (92–144)	**125** (100–157)	**103** (88–130)	**0.721**	**0.005**	**0.003**

Data are expressed as medians (range). SDNN, the standard deviation of the NN interval (all patients); SDNN* (patients without aberrant heart beats); LF_{norm}, low frequency power in normalized unit (LF/LF + HF); HF_{norm}, high frequency power in normalized unit (HF/HF + LF); LF/HF, ratio of LF component to HF component. P1: *p*-value obtained using Mann–Whitney's *U*-test. P2: *p*-value obtained using Wilcoxon test. P3: *p*-value obtained using Mann–Whitney's *U*-test.

3.1. Comparison between controls and patients with West syndrome at presentation (first EEG recording)

In the time domain, the SDNN was significantly lower in patients with WS compared to controls when awake in all patients (19.2 ms (7.6–57.2) and 31.0 ms (14.6–79.1), $p = 0.007$, Mann–Whitney's *U*-test). When comparing the patients and controls without arrhythmia the *p* value was 0.054.

In the frequency domain, only the total power was significantly lower in WS patients compared to controls (242 ms^2 (54–1643) and 659 ms^2 (167–2130), $p = 0.044$, Mann–Whitney's *U*-test). There was no significant difference in LF and LF/HF ratio.

During sleep no significant differences between groups neither in time domain parameters nor in the frequency domain were found.

A significant difference in heart rate (HR) was seen both during wakefulness and sleep in the WS patients, comparing the first EEG recording to the last with higher values at presentation with West syndrome. The patients and the controls did not differ significantly in HR neither when awake nor during sleep. The relationship between total power and HR was investigated using Pearson product-moment correlation coefficient after manual removal of extreme outliers in the patients and controls and a negative correlation between the two variables was found (WS patients: rho = −0.64, $N = 22$, $p = 0.001$, controls: rho = −0.74, $N = 20$, $p < 0.001$). However, the regression lines for the correlation between total power and HR in the two groups were different, with WS patients showing lower total power than controls in the lower range of HR (Fig. 2). To evaluate if this difference in total

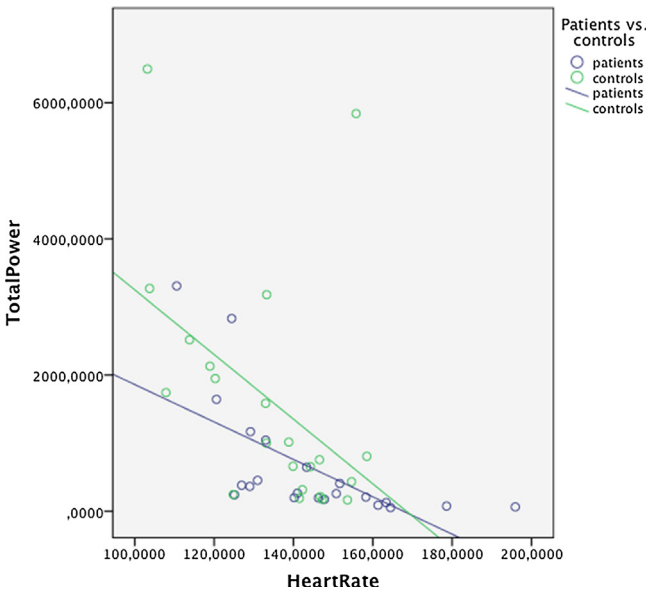

Fig. 2. Total power (ms^2) as a function of heart rate (bpm) for the patients with West syndrome (blue) and controls (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

power between patients and controls was caused by differences in HR, WS patients and controls were divided in two groups with HR < 130 and HR > 130, and total power at first examination was analysed in the two groups. A significant difference in total power between WS patients and controls was still present ($p < 0.005$, Mann–Whitney's *U*-Test).

3.2. Comparison between patients with West syndrome at presentation (first EEG recording) and at the end of the study period

At their final EEG recording patients had a median heart rate of 120 bpm (88–172) when awake and 103 bpm (88–130) during sleep.

Comparing values of the time domain parameter SDNN evolving from first to last awake EEG recording in all the patients, a significantly higher variability was seen (19.2 ms (7.6–57.2) to 31.3 ms (16.5–106), $p = 0.001$, Wilcoxon Signed Ranked Test). The same was found in the patient group without a significant amount of aberrant beats (score 0 and 1) ($p = 0.028$). Total power was higher as well (242 ms^2 (54–1643) to 757 ms^2 (192–3847), $p = 0.013$, Wilcoxon Signed Ranked Test). The change in LF_{norm}, LF/HF-ratio and HF_{norm} did not reach statistical significance ($p = 0.753$, $p = 0.463$ and $p = 0.753$) (Table 3). Also, with sleep a change during the disease course with a significantly higher value of SDNN was found (31.5 ms (12.4–75.3) to 47.4 ms (16.9–107.2), $p = 0.037$, Wilcoxon Signed Ranked Test) in the entire group of patients. In the group without a significant amount of aberrant beats, this was no longer found to be significant ($p = 0.285$).

3.3. Comparison between the patients' final EEG recording and the controls

At the time of the patients' final awake EEG recording, both SDNN and total power values had increased to levels not significantly different from those of the controls (SDNN: 31.3 ms (16.5–106) $p = 0.482$, total power: 757 ms^2 (192–3847) $p = 0.380$, Mann–Whitney's *U*-Test). The other parameters HF_{norm}, LF_{norm} and LF/HF-ratio were also comparable with the controls.

In recordings during sleep SDNN was significantly higher among the patients (31.0 ms (7.9–98.6) and 47.4 ms (16.9–107.2) $p = 0.048$). All the other HRV parameters were not significantly different from the recordings of the controls.

When investigating whether any underlying known aetiology changed the measures of HRV no difference was found in the first (total power: (922 ms^2 (655–3723) vs. 701 ms^2 (192–3847), $p = 0.270$, Mann–Whitney's *U*-Test), SDNN: (29.6 ms (26.4–63.7) vs. 27.6 ms (16.5–60), $p = 0.221$, Mann–Whitney's *U*-Test)) or the last recording (total power: 922 ms^2 (655–3723) vs. 701 ms^2 (192–3847) $p = 0.270$, SDNN: 29.6 ms (26.4–63.7) vs. 27.6 ms (16.5–60) $p = 0.211$, Mann–Whitney's *U*-Test).

Finally, no significant difference in total power during the awake state was found in patients with a good clinical outcome (242 ms^2 (64–647)) compared to patients with a poor clinical outcome at presentation (234 ms^2 (54–2832), $p = 1.000$, Mann–Whitney's *U*-test).

4. Discussion

The key finding of this study is that patients during the initial phase of West syndrome, when hypsarrhythmia is present, had reduced measures of HRV (SDNN and total power), especially when they were awake, compared to controls.

It is suggested that a reduced frequency of aberrant heart beats partly accounts for the change in variability found between study groups. The aberrant beats are considered normal findings in infants and were indeed less frequent in patients during the initial illness, when awake. We conclude that the reduced variability as well as the reduced frequency of aberrant beats are the results of a change in autonomic influence on the heart during this severe epileptic condition at the beginning of the disease.

As we find no difference in heart rate between groups, mere tachycardia could not account for the reduced variability.

With 23 patients with WS included, this cohort is the largest reported. Hattori et al. [13] also investigating autonomic function in 15 patients with West syndrome by frequency domain measures of HRV, found that patients with WS had a significantly higher low frequency (LF) power and a non-significantly higher high frequency (HF) power compared to controls. However, they also found that the distribution of LF power in the WS patients and controls overlapped, indicating that not all the patients had autonomic changes. In addition, they found no difference in LF/HF-ratio between patients and controls [13]. Contrary to their findings, we did not find a significantly lower value of LF in normalized units when awake or during sleep in WS patients compared to the controls.

Other studies have similarly shown an autonomic dysfunction in patients with other types of epileptic syndromes. Kolsal et al. [15] found reduced parasympathetic activity with lower LF and HF in 20 children with refractory epilepsy. Hallioglu et al. [9] reported significantly decreased values of SDNN interictally in 92 patients, of whom 55% had partial seizures and 41% generalized seizures. Tomson et al. [16] found a reduced HRV (SDNN and total power) and decreased low frequency power and lower LF/HF-ratio in patients with complex partial seizures with a temporal lobe focus compared to controls. This finding is similar to our finding of low LF power and lower LF/HF-ratio in patients with West syndrome compared to controls. El-Sayed et al. [17] found a decrease in SDNN in 25 epileptic children during the interictal period, where 10 patients presented generalized seizures and the rest had localization-related epilepsy. Ferri et al. [3] conducted a study of 11 children with partial epilepsy during sleep and reported an overall lower HRV in both time- and frequency-domain parameters. In contrast, Evrengul et al. [2] found an increase in SDNN in 43 patients with generalized tonic–clonic seizures. However, West syndrome is a unique electroclinical syndrome on its own.

The second important finding is that WS-patients, at the end of the acute disease course, at their final EEG recording, had recovered from the reduced HRV parameters, which were no longer significantly different from those of the controls. Actually they showed higher values of SDNN and total power especially during sleep compared to controls. This finding suggests that the abnormal autonomic cardiac influence is transient or reversible and directly related to epileptiform activity. Whether this recovery is indeed a result of disease resolution or a lingering effect from antiepileptic treatment cannot be decided.

Hattori et al. [13] showed the treatment with hydrocortisone to be correlated to an increase in HRV. The same effect could be present in our cohort. As a subgroup analysis was not possible, we could only speculate as to whether this treatment promoted the recovery of the HRV or had a lingering side effect.

We were not able to detect any prognostic significance of the initial recordings concerning neither the existence of an underlying aetiology nor the long term clinical outcome of the patients.

One limitation of this study is the lack of controlled breathing and measurement of the respiratory frequency (RF), as it is well known that RF influence heart rate variability, and especially variability in the high frequency band (HF). The WS patients and the controls did not differ significantly in HR neither when awake nor during sleep, but there was a diverging correlation between total power and HR in WS patients and controls, especially in the lower range of HR, with WS patients showing lower total power than controls. In a sub-group analysis dividing the WS patients and

controls in two groups regarding their HR, a significant difference in total power was still found between WS patients and controls in both groups, suggesting that HR is not the sole reason for differences in total power in the two groups at first examination. Individuals with the highest scores of total power and the lowest scores of HR were those with age ranging from 8 to 15 months. Age is known to influence HRV [18–20]. Massin et al. [18] found a progressive maturation of the autonomic nervous system throughout childhood in 210 healthy children aged from 3 days to 14 years and Silvetti et al. [19] investigated 103 healthy children and adolescents and found that parameters of HRV increased with age and gender. This might explain our results showing higher total power with higher age. This maturation could increase the variability during the observation period and could, therefore, account for some of the recovery of variability in the patients.

Another limitation of the study was that we did not control for the general health condition of the patients or controls, including if they were dehydrated or had electrolytic derangement, which might influence the function of the autonomic nervous system and thus the heart rate variability.

5. Summary

In the present study of time- and frequency-domain analysis of heart rate variability (HRV) obtained from a 5-min ECG recording, it was demonstrated that infants with West syndrome have reduced HRV at the onset of the disease, when hypsarrhythmia dominates, compared to controls. It was also shown, that this reduction in HRV is temporary, since at the end of the study period, there was no significant difference between WS patients and controls.

Conflict of interest

The authors declare that there are no conflicts of interest.

References

[1] Pellock JM, Hrachovy R, Shinnar S, Baram TZ, Bettis D, Dlugos DJ, et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010;51(10):2175–89.
[2] Evrengul H, Tanriverdi H, Dursunoglu D, Kaftan A, Kuru O, Unlu U, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. Epilepsy Res 2005;63(2–3):131–9.
[3] Ferri R, Curzi-Dascalova L, Arzimanoglou A, Bourgeois M, Beaud C, Nunes ML, et al. Heart rate variability during sleep in children with partial epilepsy. J Sleep Res 2002;11(2):153–60.
[4] O'Regan ME, Brown JK. Abnormalities in cardiac and respiratory function observed during seizures in childhood. Dev Med Child Neurol 2005;47(1):4–9.
[5] Devinsky O. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr 2004;4(2):43–6.
[6] Lotufo PA, Valiengo L, Bensenor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012;53(2):272–82.
[7] Scorza FA, Cysneiros RM, de Albuquerque M, Scattolini M, Arida RM. Sudden unexpected death in epilepsy: an important concern. Clinics (Sao Paulo) 2011;66(Suppl. 1):65–9.
[8] Harnod T, Yang CC, Hsin YL, Shieh KR, Wang PJ, Kuo TB. Heart rate variability in children with refractory generalized epilepsy. Seizure 2008;17(4):297–301.
[9] Hallioglu O, Okuyaz C, Mert E, Makharoblidze K. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. Epilepsy Res 2008;79(1):49–54.
[10] Jansen K, Vandeput S, Milosevic M, Ceulemans B, Van Huffel S, Brown L, et al. Autonomic effects of refractory epilepsy on heart rate variability in children: influence of intermittent vagus nerve stimulation. Dev Med Child Neurol 2011;53(12):1143–9.
[11] Yang TF, Wong TT, Chang KP, Kwan SY, Kuo WY, Lee YC, et al. Power spectrum analysis of heart rate variability in children with epilepsy. Childs Nerv Syst 2001;17(10):602–6.
[12] Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12(10):966–77.
[13] Hattori A, Hayano J, Fujimoto S, Ando N, Mizuno K, Kamei M, et al. Cardiac vagal activation by adrenocorticotropic hormone treatment in infants with West syndrome. Tohoku J Exp Med 2007;211(2):133–9.
[14] Heart rate variability. Standards of measurement, physiological interpretation, and clinical, use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17(3):354–81.
[15] Kolsal E, Serdaroglu A, Cilsal E, Kula S, Soysal AS, Kurt AN, et al. Can heart rate variability in children with epilepsy be used to predict seizures? Seizure 2014 [Epub ahead of print].
[16] Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res 1998;30(1):77–83.
[17] El-Sayed HL, Kotby AA, Tomoum HY, El-Hadidi ES, El Behery SE, El-Ganzory AM. Non-invasive assessment of cardioregulatory autonomic functions in children with epilepsy. Acta Neurol Scand 2007;115(6):377–84.
[18] Massin M, von Bernuth G. Normal ranges of heart rate variability during infancy and childhood. Pediatr Cardiol 1997;18(4):297–302.
[19] Silvetti MS, Drago F, Ragonese P. Heart rate variability in healthy children and adolescents is partially related to age and gender. Int J Cardiol 2001;81(2–3):169–74.
[20] Assaf N, Weller B, Deutsh-Castel T, Cohen A, Tirosh E. The relationship between heart rate variability and epileptiform activity among children – a controlled study. J Clin Neurophysiol 2008;25(5):317–20.